Biomedical Science

Treatment of B-cell Lymphoma Using Peptides
A Novel Concept

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Combination chemotherapy remains the major current treatment of non-Hodgkin's lymphoma. B-cell lymphoma often has tumor-specific surface immunoglobulins called idiotypes. Clinical trials using murine monoclonal anti-idiotype antibodies as a targeting approach have shown some success. I describe a novel concept of using idiotype-specific peptides as an alternative targeting approach for the treatment of B-cell lymphoma. In brief, octapeptides that bind to the surface idiotype of the B-cell lymphoma are isolated from a large synthetic peptide library (10^6 to 10^7 peptides). Once the sequence of a tumor-specific octapeptide ligand is defined, large quantities can be synthesized and conjugated with a radionuclide (such as iodine 131). This should permit highly specific destruction of lymphoma cells that bind the labeled peptide. The theoretic advantages of this approach over the previous use of anti-idiotype antibodies are addressed.

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Lymphoma, cancer of the lymphatic system, is classified as Hodgkin's disease and non-Hodgkin's lymphoma. Non-Hodgkin's lymphoma accounts for about 3% to 5% of the deaths from all human malignant neoplasms. About 35,000 new cases of the disease occur each year in the United States. The US incidence is 10.2 per 100,000 for men and 7.5 per 100,000 for women. Based on morphology, the National Cancer Institute's Working Formulation divides non-Hodgkin's lymphoma into three grades—low, intermediate, and high—with further subclassifications.[1] The low-grade form, which accounts for about 40% of all cases, is classified as "indolent" lymphoma. In general, chemotherapy has little effect on the overall survival of low-grade non-Hodgkin's lymphoma (median survival of 5 to 7 years), and the disease is rarely cured. In contrast, the intermediate- and high-grade forms behave more aggressively, but with combination chemotherapy at least 30% to 40% of patients can be cured.*

The current treatment options for non-Hodgkin's lymphoma are summarized in Table 1. Low-grade lymphoma, particularly in stages III and IV, is commonly treated only after symptoms are produced. Intermediate- or high-grade lymphoma is usually treated with conventional chemotherapy to attempt a cure. Radiation therapy may palliate or occasionally cure early stage disease.

TABLE 1.—*Current Treatment Options for Lymphoma*

No treatment
Conventional chemotherapy
Radiation therapy
Biologic therapy, such as interferon alfa
Bone marrow transplantation, autologous
Monoclonal antibody, such as anti-idiotype

Biologic therapy such as interferon alfa may be useful in low-grade lymphomas,[2] and autologous bone marrow transplantation may benefit younger patients with refractory disease.[3,4] Experimental therapy with idiotype-specific monoclonal antibody has also been tried.[5-9]

Conventional chemotherapy is always nonspecific; all chemotherapeutic drugs have substantial adverse effects on normal cells. Conventional chemotherapy preferentially kills proliferating cells, which include those of the normal gastrointestinal tract, hair follicles, and the hematopoietic system. Consequently, chemotherapy often leads to notable side effects such as hair loss, gastrointestinal toxicity, nausea, vomiting, neutropenia, thrombocytopenia, and anemia. The toxicity of certain chemotherapeutic drugs may affect specific organs, such as toxicity of doxorubicin on the heart and that of bleomycin on the lungs. In contrast, antibiotics are far more specific in their action against bacteria and do not usually affect normal cells. This results in a high therapeutic index and a high curative rate for most bacterial infec-

*See also the editorial by M. F. Renschler, MD, and R. Levy, MD, "Overcoming the Limitations of Chemotherapy in the Treatment of B-cell Non-Hodgkin's Lymphomas—An Approach Using Radiolabeled Peptide Ligands," on pages 530-532 of this issue.

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tions. Conventional chemotherapy has a narrow therapeutic index, and high doses can be administered only if the cells of the bone marrow can be replaced by transplantation.[3,4]

About 85% of cases of non-Hodgkin's lymphoma originate in B cells. B-cell lymphomas are unique in that many have monoclonal surface immunoglobulins, called idiotypes (Figure 1). The idiotype, specific to that tumor clone, is the only true "tumor-specific antigen." Levy

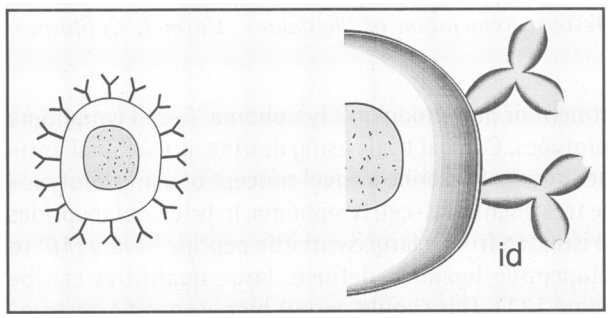

Figure 1.—The diagrams show the cell surface antibody idiotype **(id)** of B-cell lymphoma.

and co-workers pioneered in the treatment of B-cell lymphomas with murine monoclonal anti-idiotypic antibodies that are directed against these surface idiotypes.[4-8] Patients with non-Hodgkin's lymphoma have been treated with anti-idiotype antibodies alone, in combination with interferon alfa, or in combination with chlorambucil.[9] The use of anti-idiotype antibody alone (16 treatment courses) was associated with two complete responses and six partial responses. Although most of the relapsing tumors expressed surface immunoglobulin, in only five of the ten analyzed did the tumor cells react with the original anti-idiotype antibody.[9,10] Two patients with B-cell lymphoma have been treated with anti-idiotype monoclonal antibody labeled with yttrium 90.[11] This approach can potentially circumvent the emergence of idiotype-negative tumor cells because these cells may also be killed as bystanders within the tumor mass. Besides anti-idiotype therapy, therapy with pan-B–reactive murine antibody has also been tried in both the unconjugated[12] and iodinated (iodine 131) forms.[13]

To increase the therapeutic potency of monoclonal antibodies, cytotoxic agents such as chemotherapeutic drugs, toxins, or radionuclides have been coupled to the monoclonal antibodies.[14] For immunotoxins, ricin A chain, diphtheria toxin, and *Pseudomonas* exotoxin A have been most commonly used. Radionuclides such as yttrium 90, bismuth 212, iodine 125, and iodine 131 have all been used to conjugate to antibodies for immunotherapy.

Concept of Antigen-Directed Immunotherapy

Instead of using anti-idiotype monoclonal antibodies for the treatment of B-cell lymphomas, it is conceivable that a specific antigen-immunotoxin conjugate or radioactive antigen could be used that would target the surface idiotype of the lymphoma cells (Figure 2). This would permit highly specific destruction of the lymphoma cells capable of binding these labeled antigens. This concept of "antigen-directed immunotherapy" is not new; an [^{125}I]dinitrophenylated L-Tyr-L-Glu-L-Lys copolymer antigen of high specific activity has been used to deplete an antidinitrophenyl B-cell clone.[15] An ^{125}I-labeled liver-specific antigen has been used to inhibit the development of experimental autoimmune hepatitis in rabbits,[16] and an ^{125}I-labeled acetylcholine receptor has been used to reduce the severity of experimental autoimmune myasthenia gravis (EAMG) in rats.[17] Antigen-ricin A chain conjugates have been used to selectively inhibit antinucleoside-specific antibody production,[18] antithyroglobulin autoantibody response,[19] anti-tetanus toxoid antibody production,[20] and antiacetylcholine receptor response in EAMG.[21,22] The efficacy of antigen-directed immunotherapy has therefore been well established in various experimental systems. The treatment of chronic EAMG with antigen-toxin conjugates or radiolabeled conjugates has proved more difficult.[23] The antigen used was a macromolecule (in this case acetylcholine receptor), and its use resulted in the formation of large aggregates and nonspecific toxicity of the conjugates in tissues in which the aggregates collect. Nonspecific toxicity was also seen with antibody-immunotoxin conjugates as described earlier.

Synthesizing and Identifying a Mimotope

The major obstacle to the concept of antigen-directed immunotherapy in B-cell lymphoma is finding the antigen to which the idiotype specifically binds. That is, a "mimotope" must be found that binds to the antigen-

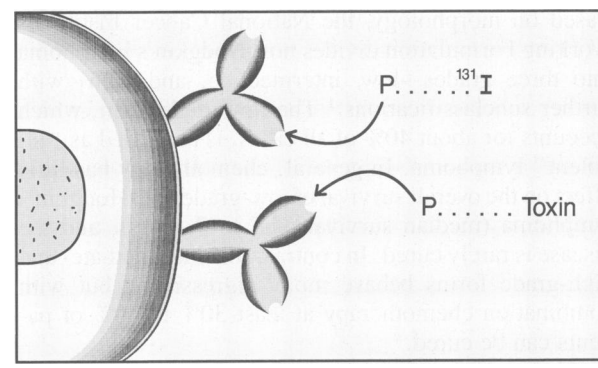

Figure 2.—Once identified, the idiotype-specific peptide **(P)** can be conjugated to either iodine 131 or a toxin for targeted therapy.

combining site of the surface idiotype. (Mimotope is defined as an amino acid sequence that will mimic the antigenic site and that will bind specifically to the antigen-combining site of the antibody molecule.) Ideally this would be accomplished by rapidly selecting the required mimotope from a large library of peptides. Such a task is enormous even for short peptides. Figure 3 shows the possible number of permutations for peptides of various lengths when all 20 L-amino acids are used in the synthesis of such a library. Even for a pentapeptide, there are 3.2×10^6 possible permutations. Synthesizing

such a library one peptide at a time is practically impossible, but substantial technical advances have been made in this area in the past five years. A system has been devised to synthesize peptides on polyethylene pins for mapping epitopes and determining mimotopes.[24] As another approach, randomly generated DNA fragments have been inserted into gene III of a filamentous bacteriophage for generating peptide libraries.[25-27] From such large phage-peptide libraries, ligands specific to two antimyohemoerythrin monoclonal antibodies,[25] an anti-β-endorphin monoclonal antibody,[26] and streptavidin[27] have been identified. Peptide ligands specific to concanavalin A have been identified using the same technique.[28,29] A technique of light-directed, spatially addressable parallel chemical synthesis of an array of 1,024 peptides simultaneously on a glass microscope slide has been developed.[30] A solution of an equimolar mixture of peptides has been generated, and the investi-

X	$20^1 = 20$
XX	$20^2 = 400$
XXX	$20^3 = 8{,}000$
XXXX	$20^4 = 160{,}000$
XXXXX	$20^5 = 3{,}200{,}000$
XXXXXX	$20^6 = 64{,}000{,}000$
XXXXXXX	$20^7 = 1{,}280{,}000{,}000$

Figure 3.—The number of possible permutations are shown for a random peptide if all 20 L-amino acids are used.

gators proposed the concept of using such a library for drug discovery.[31] A combinatorial peptide library approach to identify peptide ligands that interact with a monoclonal antibody has been described.[32]

These previously described techniques have biologic, chemical, and practical limitations that have led to an exploration of more powerful alternative approaches to synthesize and screen peptide libraries. A simple method—"selectide technology"—has been devised that greatly facilitates the chemical production and rapid evaluation of random libraries of millions of peptides.[33] This should allow the rapid identification and sequencing of peptide ligands that bind to acceptor molecules such as the lymphoma surface idiotype. Such an acceptor molecule, defined as a macromolecule that interacts specifically with ligands, could be an antibody, an enzyme, or a biologic receptor molecule.

Briefly, in selectide technology, a "split-synthesis" method is used to synthesize on solid-phase beads a large library of peptides (1 to 10 million). In the resultant peptide library, each individual bead represents only one peptide entity (the one-bead, one-peptide concept). The peptide library is incubated with an enzyme-labeled monoclonal antibody (such as alkaline phosphatase conjugate). After thorough washing, a chromogenic substrate—for example, 5-bromo-4-chloro-3-indolyl phosphate and nitroblue tetrazolium—is added. The peptide bead that reacts with the monoclonal antibody turns dark blue. The blue bead is then physically isolated and the amino acid sequence of the mimotope determined with a protein microsequencer.[33]

In one set of experiments, a large, synthetic, random pentapeptide library was generated: XXXXX-β-ala-aminocaproic acid-ethylenediamine-resin, where X represents the 19 eukaryotic amino acids, excluding cysteine, with a total of approximately 2.5 million permutations. The monoclonal antibody used to screen the library was anti-β-endorphin. From a library of about 2 million beads, six peptide ligands were identified, all of which have close resemblance to the native ligand. Importantly, the affinity constants of three of these six selected ligands are as good as that of the natural ligand.

I plan to apply this new method to identify a peptide that has high affinity for the surface idiotype of a B-cell lymphoma and then to use that peptide for targeting treatment.

Possible Advantages of Antigen-Directed Immunotherapy

For an individualized treatment program such as the one proposed here, it is important that it can be created without undue delay. Once our methods are established, the timing should be reasonably rapid, especially with the selectide technique. Once the sequence of the mimotope is identified, large quantities of an octapeptide can be rapidly synthesized. The total time required is anticipated to be less than a month. This is considerably shorter and more economic than creating mouse monoclonal anti-idiotype antibodies (which takes 12 to 14 months).[9]

In addition to speed, the concept of antigen-directed immunotherapy using small peptides offers several distinct therapeutic advantages over the use of anti-idiotype monoclonal antibodies (Table 2):

- The peptide-conjugate will be considerably smaller than the antibody conjugate, which should allow better tissue penetration;
- Large quantities of the peptide-conjugate (such as [^{131}I]peptide) can easily be synthesized with high specific activity;
- The reticuloendothelial system uptake of the peptide-conjugate will likely be less than that of the antibody-conjugate;
- Because of its small size, the peptide-conjugate, especially the radioactive peptide, may not be immunogenic, and hence a host antibody reaction may not occur;
- D-Amino acids can be used in the peptide-conjugate synthesis and will not be readily hydrolyzed in the body;
- Using techniques in modern synthetic peptide chemistry,[34] we can modify peptide sequences with unnatural amino acid analogues and possibly increase their affinity for the idiotype, thereby increasing the therapeutic index and improving its pharmacokinetic properties.

Figure 4 summarizes a proposed scheme for the generation of lymphoma-binding peptides for antigen-

TABLE 2.—*Peptide Mimotope Compared With Murine Anti-idiotype Monoclonal Antibody as Therapy Targeted Against B-cell Lymphoma*

Therapy	Molecular Weight	Tissue Penetration	Therapeutic Quantity	Chemical Modification*	Reticulo-endothelial System Uptake	Immunogenic	Higher-Affinity Analogues	Time From Biopsy to Treatment
Peptide mimotope	600-1,000	Superior	Quick and inexpensive	Easy	Negligible	Probably not	Easier	2-3 wk†
Anti-idiotype monoclonal antibody	160,000	May be a problem	Slow and expensive	Difficult	High	Possibly a problem‡	Difficult	1 yr

*An example would be radiolabeling.
†This is still theoretic.
‡Human antimouse antibody.

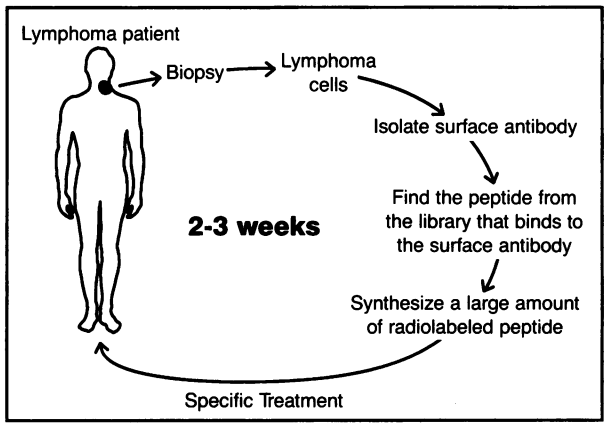

Figure 4.—A hypothetic scheme is shown for developing idiotype specific for the treatment of B-cell lymphoma peptide.

directed radioimmunotherapy. Work currently underway in my laboratory will determine peptide mimotopes for both human and murine B-cell lymphoma cell lines. Clinical trials will begin only after efficacy has been proved both in vitro and in vivo in the murine model. Antigen-directed immunotherapy is not restricted to the treatment of B-cell lymphoma. Target cells other than of B-cell lymphoma could include those of T-cell lymphoma, chronic lymphocytic leukemia, or acute lymphocytic leukemia provided that these neoplastic cells have surface idiotypes. In addition, a number of other possible applications of this technology include eliminating the B-cell clones that cause various autoimmune diseases.

Questions and Answers

PHYSICIAN IN THE AUDIENCE: *How can you conveniently deliver the radioactive peptide to a patient?*

DR LAM: For L-amino acid–containing peptides, gastrointestinal uptake will not be practical because the peptides would be degraded. Furthermore, there are no transport systems for these peptides across the epithelial cells. An intravenous administration would be used initially for peptides previously radiolabeled and purified in the laboratory.

PHYSICIAN IN THE AUDIENCE: *Have you been able to identify a peptide that has high affinity for lymphoma idiotypes? If so, does it have the same affinity as you have shown for the anti-β-endorphin monoclonal antibody?*

DR LAM: We are currently perfecting the technique of isolating peptides, and we are just beginning to work on human and mouse lymphoma cell lines. I hope that in a few months we can answer that question.

PHYSICIAN IN THE AUDIENCE: *In his comparable work, Ronald Levy, MD, has faced two problems that you will face as well. First, will even the smaller molecules find their way through tumor tissue that is necrotic and poorly perfused? The second question concerns the specificity of killing cells with an agent tagged with something like ^{131}I or any agent that releases a penetrating γ-ray. The experience has been that no matter how specific the monoclonal antibody, the whole body is affected by radiotherapy because of the penetration of the γ-rays. So you will need an agent with a narrow emitter for killing cells, which may have to be a β-particle. Finally, B cells have an unfortunate tendency to mutate. As a result, something that may have been specific at one time will lose its effectiveness based on its inability to bind with the mutated receptor molecule. One may therefore need a cocktail or a constantly changing mixture of specific materials. The method remains innovative, however, and we thank you for that.*

DR LAM: We chose ^{131}I for initial studies because it is relatively easy to synthesize an [^{131}I]peptide in the laboratory. We can use another radionuclide that has a shorter range of radiation, however, so that it will not affect other cells. I think that the key reason that radiolabeled monoclonal antibodies affect the whole body is that the reticuloendothelial cells of the liver, spleen, and bone marrow reticulum take up the derivatized antibody. We hope that small peptides will bind only to the lymphoma target and that any unbound peptide will be rapidly excreted by the kidney. This has certainly been true for the use of ^{131}I to ablate the thyroid. As you have correctly pointed out, B-cell tumors have regressed, only to recur with an altered idiotype, usually in either the light chain or the heavy chain, but not both. We hope that the use of a radioactive peptide will also kill any mutated bystander cells with altered idiotype. In addition, because the peptide actually fits into the antigen-combining site (paratope) of the antibody molecule, it is conceivable that despite the mutation of one chain, the hypervariable region of the other chain may retain sufficient functional contact groups for the peptide mimotope to interact. In other words, the mimotopes may still be able to bind to the new paratope, although perhaps with a somewhat lower affinity. Furthermore, there are shared idiotypes.[35] Therefore, instead of using individualized treatment programs for

patients, a select panel of perhaps 20 or 30 peptides might prove sufficient to treat a relatively wide range of lymphoma cells. A combination of various peptide approaches is another possibility. All of the potential problems that you raise are definitely valid and need to be addressed.

It is also unclear what would happen when an unlabeled peptide binds to the lymphoma cell. Will the peptide enter the cell and subsequently present in a class I antigen, perhaps to be seen by a T cell, with killing of the presenting cell? Will the cell automatically undergo apoptosis? All of these questions still have to be worked out if we are to develop a truly specific targeting approach for treating B-cell lymphoma.

PHYSICIAN IN THE AUDIENCE: *Are your B-cell lymphomas monoclonal, oligoclonal, or polyclonal?*

DR LAM: For B-cell lymphoma unrelated to the acquired immunodeficiency syndrome, they are monoclonal, at least in the early stage. As noted earlier, following treatment with murine anti-idiotype antibodies, tumors will regress, but they may recur with a changed idiotype—that is, a new clone.

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